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18 May 2005

By Fax

Dear Sirs

International Patent Application No. PCT/GB2004/002905
University Court Of The University of St Andrews
"Delivery of Nitric Oxide"

In reply to the Written Opinion of the International Searching Authority, mailed on 10 November 2004, we confirm that a Demand for International Preliminary Examination was filed with our letter dated 3 May 2005, and we enclose herewith amended claims 1-40.

We reply to the Written Opinion as follows.

Claims 1 to 8 relate to a zeolite material comprising releasably adsorbed nitric oxide for use in surgery and/or therapy.

Claim 9 relates to a pharmaceutical preparation comprising a zeolite material comprising releasably adsorbed nitric oxide.

Claims 10 to 18 relate to the use of a zeolite material comprising releasably adsorbed nitric oxide in the preparation of a medicament for use in treatment or prophylaxis of disease.

Claims 19 and 20 relate to a medical article comprising a zeolite material which comprises releasably adsorbed nitric oxide.

Claim 21 relates to the use of a zeolite comprising releaseably adsorbed nitric oxide in a cosmetic and/or personal hygiene application.

Claims 22 to 30 relate to a cosmetic and/or personal hygiene product comprising a zeolite which comprises releasably adsorbed nitric oxide.

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Claims 31 to 36 relate to a method of preparing a medical article, cosmetic and/or personal hygiene product.

Claims 37 to 39 relate to a method of releasing nitric oxide from the zeolite material inside an animal body or in non-body applications, which includes release into cell cultures.

Claim 40 relates to a method of treatment or prophylaxis.

The basis for the claims provided herewith is identified in the table on the additional sheet enclosed herewith.

The term "restonsis" in claim 18 has been corrected to read "restenosis" which would be immediately apparent to the skilled person as the correct term, which is used at page 10, line 24 of the description. Page 11, line 24 of the description has likewise been amended and which is enclosed herewith as a replacement page.

Novelty

Claims 1 to 8, 9, 10 to 18, 19, 20, 31 to 36 (as regards a medical article), 37 to 39 and 40.

None of the cited prior art discloses or describes zeolite materials comprising releasably adsorbed nitric oxide for the stated uses and applications in the above-listed claims.

Specifically, those claims relate to medical applications of zeolite materials which comprise releasably adsorbed nitric oxide. The prior art also does not disclose methods of preparing the claimed medical articles.

Applicant draws the Examiner's attention to previous claim 20 which related to a medical article comprising a zeolite material without nitric oxide loaded therein. That claim has now been deleted. Previous claim 19 has also been deleted.

Accordingly, the above-referenced claims are novel over the cited prior art.

Claims 21, 22 to 30 and 31 to 36 (as regards a cosmetic and/or personal hygiene product).

None of the cited prior art discloses or describes zeolite materials comprising releasably adsorbed nitric oxide for the stated uses and applications directed to cosmetic and/or personal hygiene products. The prior art also does not disclose methods of preparing the claimed cosmetic and/or personal hygiene products.

Accordingly, the above-referenced claims are novel over the cited prior art.

Inventive Step

Claims 1 to 8, 9, 10 to 18, 19, 20, 31 to 36 (as regards a medical article), 37 to 39 and 40.

Claim 1 corresponds to previous claim 15 and the Examiner has considered that in view of D7 and D2 in combination an inventive step is not acknowledged.

The Applicant respectfully disagrees because document D7 is concerned with prolonging the release of nitric oxide from a polymer adduct and, it is stated at page 10, lines 3-8 that N₂O₂- groups near the surface are available for rapid release while those deeply embedded require more time and/or energy for the nitric oxide to be released.

Additionally, it is stated in D7 at page 10, lines 9-12 that increasing the positive charge near the N₂O₂- group increases the half-life of nitric oxide generation, i.e. increases the release time.

Thus, D7 is teaching the skilled person to make use of the polymeric materials disclosed therein, and provides a rational as to why those materials should be used. D7 positively motivates the skilled person to use those polymeric materials. Because D7 positively encourages the skilled person to use the polymers disclosed therein, D7 does not direct the skilled person to consider using alternative methods of nitric oxide delivery

Accordingly, the skilled person has no reason to change the materials described in D7 and thus would not be motivated to review literature to identify alternative nitric oxide delivery methods, and accordingly, the skilled person would not be motivated to seek alternative materials to those of D7.

Furthermore, document D7 is entirely concerned with delivery of nitric oxide by way of a nitric oxide-releasing functional chemical group, i.e. N₂O₂- which is bound to a polymer. This mechanism of storage and delivery is quite different to that of a zeolite comprising adsorbed nitric oxide. This is because, the nitric oxide adsorbed in a zeolite is not derivatised as a distinctly different functional group, but rather, the molecule of nitric oxide, i.e. NO is held within the zeolite framework and is not chemically changed into a functional group, which must undergo a chemical reaction before nitric oxide is released. Instead the nitric oxide in a zeolite framework is released by simple disruption of the bonds which temporarily anchor it within the zeolite framework.

Thus, even if the skilled person was directed to document D2, there is no indication in that document that the nitric oxide adsorbed zeolites described therein would fulfil the requirements of the nitric oxide-releasing materials of document D7. In this regard, D7 specifies that the nitric oxide-releasing N₂O₂- functional groups that are bound to the polymer generally are capable of releasing nitric oxide in an aqueous environment.

In contrast, document D2 is not concerned with release into an aqueous environment because D2 relates to the reversible and irreversible adsorption of nitric oxide for the removal of low concentration nitric oxide, and in the description experiment cited by the Examiner (page 2338, left hand column) no method of nitric oxide release into an aqueous environment is described or contemplated. All that D2 shows is that a zeolite

material which is first loaded with nitric oxide can thereafter release the nitric oxide **when placed in a flow of helium gas.**

Thus, D2 does not add to the teaching of document D7 to arrive at the invention **as claimed in claim 1**, which is directed to a zeolite comprising releasably adsorbed nitric oxide for use in surgery and/or therapy. This is because D7 does not motivate or **direct** the skilled person to use a nitric oxide loaded zeolite material, and furthermore, D2 does not provide a technical teaching that a nitric oxide loaded zeolite may be used to **release nitric oxide in an amount, rate and suitably controlled manner into an external medium to enable its effective use in surgery and/or therapy.** The Applicant considers that **at least, the Examiner has used unallowable hindsight to deny an inventive step**

Accordingly, claim 1 is considered to involve an inventive step over D7 in combination with D2.

Claims 2 to 8, being dependent on claim 1 are also therefore considered to **involve an inventive step.**

Claim 9, relating to a pharmaceutical preparation is also considered to **involve an inventive step** for the reasons given above.

Claims 10-18, relating to the use of a zeolite as recited in those claims are also **considered to involve an inventive step** for the above reasons.

Likewise, claims 37-39 and 40 are also considered to involve an inventive step.

Claims 31-36, in respect of relating to a method of preparing a medical article **are considered to involve an inventive step**, as the prior art nowhere teaches or **suggests providing a medical article which comprises a zeolite without adsorbed nitric oxide and then contacting the medical article with nitric oxide gas.**

Accordingly, claims 31-36 are considered to involve an inventive step.

Claims 21, 22 to 30 and 31 to 36 (as regards a cosmetic and/or personal hygiene product).

Claim 21 corresponds to previous claim 23 and relates to the use of a zeolite comprising releasably adsorbed nitric oxide in a cosmetic and/or personal hygiene application.

The Examiner considers D8 as the closest prior art to this subject matter, and concludes that in view of D8 in combination with D2, an inventive step is not acknowledged.

Document D8 discloses a composition containing a nitric oxide liberating compound. D8 does not disclose a zeolite material comprising releasably adsorbed nitric oxide. The Examiner alleges that D8 discloses that the compounds therein liberate NO either spontaneously or under a biochemical or physical influence. However, D8 goes no further than that teaching and provides no motivation to the skilled person to seek alternative materials to those disclosed in D8. Accordingly, the skilled person is not taught to

consider using for cosmetic/personal hygiene applications, a zeolite material comprising releasably adsorbed nitric oxide.

In particular, the skilled person is not directed to consider document D2. Furthermore, even if the skilled person was directed to document D2, there is no indication in that document that the nitric oxide adsorbed zeolites described therein would fulfil the requirements of the nitric oxide-releasing materials of document D8 for cosmetic and/or personal hygiene applications.

Document D2 is only concerned with a zeolite material which is first loaded with nitric oxide which can thereafter release the nitric oxide when placed in a flow of helium gas.

Thus, D2 does not add to the teaching of document D8 to arrive at the invention as claimed in claim 21. This is because D8 does not motivate or direct the skilled person to use a nitric oxide loaded zeolite material, and furthermore, D2 does not provide a technical teaching that a nitric oxide loaded zeolite may be used to release nitric oxide in an amount, rate and suitably controlled manner into an external medium to enable its effective use in cosmetic and/or personal hygiene applications.

The Applicant considers that, at least, the Examiner has used unallowable hindsight to deny an inventive step.

Accordingly, claim 21 is considered to involve an inventive step over D8 in combination with D2.

Independent claim 22, and dependent claims 23-30 are directed to a cosmetic and/or personal hygiene product comprising a zeolite which comprises releasably adsorbed nitric oxide, and are also considered to involve an inventive step over D8 in combination with D2.

Claim 31, and dependent claims 32-36 as regards a method of preparing a cosmetic and/or personal hygiene product are also considered to involve an inventive step, as the prior art nowhere teaches or suggests providing a cosmetic and/or personal hygiene product which comprises a zeolite without adsorbed nitric oxide and then contacting the said product with nitric oxide gas.

Accordingly, the Applicant awaits a favourable further Written Opinion or International Preliminary Report on Patentability.

Yours faithfully


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Enc. Amended claims 1-40.

Page 11.

Additional Sheet

Basis for the Claims

<u>Claim</u>	<u>Basis</u>
Claim 1	Previous claim 15.
Claims 2-4	Previous claims 2-4.
Claim 5	Description as originally filed at page 22, lines 6 et seq, and Figures 4 and 5 referred to therin which disclose the specific zeolite types recited in claim 14.
Claims 6-8	Previous claims 5-7.
Claim 9	Previous claim 16.
Claim 10	Previous claim 17.
Claims 11-13	Previous claims 2-4.
Claim 14	Description as originally filed at page 22, lines 6 et seq, and Figures 4 and 5 referred to therein which disclose the specific zeolite types recited in claim 14.
Claims 15-17	Previous claims 5-7
Claim 18	Previous claim 18.
Claim 19	Previous claim 21.
Claim 20	Previous claim 22.
Claim 21	Previous 23.
Claim 22	Previous claim 24.
Claims 23-25	Previous claims 2-4.
Claim 26	Description as originally filed at page 22, lines 6 et seq, and Figures 4 and 5 referred to therein which disclose the specific zeolite types recited in claim 14.
Claims 27-29	Previous claims 5-7.
Claim 30	Previous claim 25.
Claim 31	Previous claim 9 and the description as originally filed at page 10, lines 25-27.
Claims 32-36	Previous claims 10-14.
Claim 37	Previous claims 26 and 28.
Claims 38-40	Previous claims 29-31.

for example, for suppository application in the treatment of severe constipation.

According to a third aspect of the present invention
5 there is provided a zeolite material comprising releasably adsorbed nitric oxide for use in surgery and/or therapy.

According to a fourth aspect of the present invention
there is provided a pharmaceutical, neutraceutical or
cosmetic preparation comprising a zeolite material
10 comprising releasably adsorbed nitric oxide together with
a pharmaceutical/neutraceutical/cosmetic carrier therefor.

The present invention also provides the use of a
zeolite material comprising releasably adsorbed nitric
oxide in the preparation of a medicament for use in the
15 treatment or prophylaxis of disease.

Diseases or medical conditions which may be treated
include infections of the skin, including dermatophyte
fungi, leishmaniasis, molluscum and papilloma virus, and
mycobacterium infections. Further uses include therapeutic
20 applications in anti-neoplastic activities, immune
response modification, treatment of Raynaud's disease,
wound healing and skin pigment modification. Yet further
uses include treatment of restenosis, psoriasis and
eczema, and skin cancer (melanoma). Therapies for other
25 bacterial problems include the reduction of severe foot or
body odour problems, and in the treatment of Methicillin
Resistant Staphylococcus Aureus infections.

According to a sixth aspect of the present invention
there is provided a medical article comprising a zeolite
30 material.

The zeolite material of the medical article may be
provided without nitric oxide loaded therein to allow

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